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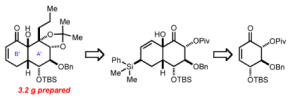
Benjamin C. Milgram, **Brian B. Liau**, and **Matthew D. Shair***
Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Abstract



A gram-scale enantiospecific synthesis of the A'B'-subunit of angelmicin B is reported. The synthesis involves a Lewis acid-catalyzed contrasteric Diels–Alder reaction and a tandem silyl zincate 1,6-addition/enolate oxidation sequence.

Angelmicin B (**1**, Figure 1) was isolated in 1993 by Uehara, Oki, and coworkers from the rare actinomycete *Microbispora* subsp. AA9966.[1,2] Hibarimicin B, which was subsequently isolated along with hibarimicin A-G from the *Microbispora rosea* subsp. *hibaria* TP-A0121, shares an identical structure with **1**. Angelmicin B (**1**) was originally identified as an inhibitor of Src tyrosine kinase (IC_{50} > 5800 nM),[1a] and was later found to inhibit proliferation and induce differentiation of HL-60 human leukemia tumor cells (IC_{50} = 58 nM).[3] The discrepancy between these effective concentrations suggests that Src is perhaps not the target responsible for the anticancer activity of **1**, and to date, the cellular target of **1** remains unidentified.

Angelmicin B (**1**) is a pseudo-C_2-symmetric glycosylated type II polyketide. The two halves of its fascinating pseudo-C_2-symmetric structure differ in the oxidation states of the B/B', C/C', and D/D' rings. Several questions concerning the absolute and relative configuration of **1** remain to be addressed.[4] The absolute configuration of both halves of the aglycon and the carbohydrates as well as the relative stereochemistry of the C13′-carbinol are unknown. Additionally, it is unclear whether the compound exhibits atropisomerism as a result of potential hindered rotation about its C2–C2′ bond.[5] A total synthesis of **1** or its aglycon would elucidate these stereochemical uncertainties, but has yet to be achieved.[6] Intrigued by the biological properties, stereochemical ambiguities, and structural complexity of **1**, we initiated a program aimed at its total synthesis. Herein we report a highly scalable enantiospecific synthesis of the orthogonally protected A'B'-subunit of angelmicin B (**2**, Scheme 1).

Our retrosynthesis of **2** is outlined in Scheme 1. We anticipated that the enone functionality in **2** could be generated by oxidation of allylic silane **3**. Additionally, we envisioned that introduction of the *n*-propyl substituent in **2** could be accomplished through a diastereoselective organometallic addition to α-hydroxy ketone **3** from the convex face of the rigid *cis*-decalin carbon framework. Next, compound **3** would be accessed by means of a

*shair@chemistry.harvard.edu .

Supporting Information Available: Experimental procedures, physical data, X-ray data for compound **2**, and copies of ^1H and ^{13}C spectra for compounds **2**–**5**, **7**, **8**, **11**, **14**, **15**, and all synthesis intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

regio- and diastereoselective 1,6-addition of a silyl zincate to dienone **4**, followed by in situ oxidation of the resultant extended zinc enolate. A Lewis acid-catalyzed contrasteric Diels–Alder reaction between cyclohexenone **5** and 1,3-butadiene would then set the relative stereochemistry in **4**, wherein the newly formed C–C bonds and the C4–OTBS substituent reside in a *syn* orientation. Finally, suitably protected cyclohexenone **5** would be prepared through ring-closing metathesis of a linear precursor accessed from readily available D-glucose derivative **6**. The type and position of the hydroxyl protecting groups were chosen with respect to two criteria. First, a C4–OTBS group was deemed necessary for *syn* selectivity in the key Lewis acid-catalyzed contrasteric Diels–Alder reaction. Second, orthogonally deprotectable groups were selected to facilitate sequential introduction of the sugar residues surrounding angelmicin B. The ability to produce gram quantities of late-stage intermediates is essential for a successful total synthesis of angelmicin B, one of the largest and most complex aromatic polyketides known. Recognition of the common stereochemical elements shared by **2** and D-glucose helped enable the realization of this requirement.

Our synthesis commenced with compound **6**, which was obtained in three steps from methyl α-D-glucopyranoside on multigram scale according to a modified literature protocol (Scheme 2).[7] A three-step procedure for the conversion of **6** to iodide **7** began with AcOH-mediated hydrolysis of the benzylidene acetal, followed by selective Wittig iodination of the resultant primary hydroxyl group and TBS protection of the remaining secondary carbinol in 90% overall yield. Sonication of **7** with activated zinc powder promoted reductive fragmentation to generate an aldehyde intermediate,[8] which upon treatment with an organocerium reagent derived from vinylmagnesium bromide furnished allylic alcohol **8** as an inconsequential diastereomeric mixture in 75% yield over two steps.[9,10] Finally, exposure of **8** to first-generation Grubbs olefin metathesis catalyst[11] in dilute CH_2Cl_2 followed by Parikh–Doering oxidation[12] of the resulting diastereomeric cyclohexenols produced cyclohexenone **5** in 82% yield over two steps. Over thirty grams of **5** was prepared through this method.

Following our synthesis of **5**, we next attempted the key Lewis acid-catalyzed contrasteric Diels–Alder reaction depicted in eq 1 of Scheme 3. Danishefsky and coworkers had previously demonstrated that 2-cyclohexenone **9**, bearing a γ-OTBS group, participates in a contrasteric intermolecular Diels–Alder reaction with 1,3-butadiene when catalyzed by $AlCl_3$ to provide *cis*-decalin **10** in 76% yield (eq 1, Scheme 3).[13] In this transformation, the β-C–C bond is formed *syn* relative to the γ-OTBS group in high diastereoselectivity (>10:1 *syn*:*anti*). We anticipated similar stereoselectivity in our proposed Diels–Alder reaction, despite the additional Lewis basic groups in our substrate. Gratifyingly, treatment of **5** with 1,3-butadiene in the presence of $TiCl_4$ at **5** °C for 3.5 h afforded a >10:1 mixture of adducts, favoring the desired *syn* diastereomer **11**. This reaction, which can be performed on multigram scale with high diastereoselectivity, is to our knowledge the most complex example of a contrasteric Diels–Alder yet reported.

The stereoselectivity of this reaction is likely governed by subtle steric and stereoelectronic effects. Approach of 1,3-butadiene to **5** *syn* to the γ-OTBS substituent is sterically occluded by both the γ-OTBS and α-OPiv groups and thus counterintuitive (transition state 1, Scheme 3). However, stereoelectronic considerations suggest that pseudo-axial approach of 1,3-butadiene to the β-carbon of the chair-like ground state conformation of **9** is kinetically favored.[14] Additionally, the Cieplak model has been invoked to rationalize the stereochemical outcome for the aforementioned Diels–Alder reaction.[15] In accordance with this line of reasoning, formation of the β-C–C bond *syn* with the electron-withdrawing γ-OTBS group stabilizes the forming σ*-C–C orbital through hyperconjugation with the electron-donating σ-C–H bond (transition state 2, Scheme 3). It is plausible that a synergism

of individually small stereoelectronic effects bias the reaction pathway towards the observed product diastereomer **11**.

The synthesis of **2** continued with a series of carefully controlled oxidations of the *cis*-decalin carbon skeleton of **11** (Scheme 4). Exposure of **11** to TMSI, generated in situ from TMSCl and NaI, promoted thermodynamic enolization of the ketone at C6 rather than at C2 to generate enol silane **12** as a single regioisomer.[16] This regioselection is particularly noteworthy since C2–H is presumably more acidic than C6–H. Chemoselective oxidation of **12** was accomplished upon treatment of **12** with DDQ to afford dienone **4** in 78% overall yield, again as a single regioisomer.[17] The mild nature of this procedure prevented over-oxidation of the dienone moiety. Next, regio- and diastereoselective addition of dimethylphenylsilyl zincate to the δ-position of dienone **4** generated extended zinc enolate intermediate **13**.[18] In situ α-oxidation of **13** with MoO_5•pyr•HMPA (MoOPH) delivered *cis*-decalin **3** as a single regio- and diastereoisomer in 82% yield. The one-pot 1,6-conjugate addition/enolate oxidation sequence was amenable to a variety of oxidants including Davis oxaziridine and DMDO; however, MoOPH proved the most efficient oxidant on large-scale.[19] Overall, the tandem reaction sequence generated the sterically congested C6-tertiary carbinol and an allylic silane, which was planned to serve as a latent enone surrogate.

Exposure of **3** to excess organocerium reagent derived from *n*-propylmagnesium chloride led to carbonyl addition exclusively from the convex face of the molecule and concurrent cleavage of the pivoyl ester (Scheme 4).[20] The use of a mixed organocerium reagent was required to avoid ketone enolization and reduction.[21] The resultant 1,2-diol was protected as an acetonide, affording **14** in 71% yield over two steps. Treatment of **14** with *m*-CPBA led to epoxidation of the allylic silane with in situ 1,5-silyl migration of silicon and concomitant epoxide opening to provide compound **15** in 85% yield.[22] Chemoselective removal of the dimethylphenylsilyl group with TBAF at −78 °C and Swern oxidation[23] of the resulting allylic alcohol delivered **2** in 91% yield over two steps on gram-scale, completing our synthesis of the protected A'B'-subunit of angelmicin B.

In summary, a scalable and enantiospecific synthesis of the protected A'B'-subunit of angelmicin B (**2**) has been accomplished starting from methyl α-D-glucopyranoside. This sequence has been utilized to prepare 3.2 grams of **2** to date. The synthesis features a Lewis acid-catalyzed contrasteric Diels–Alder reaction between cyclohexenone **5** and 1,3-butadiene. Additionally, the synthesis further demonstrates the utility of silyl zincate reagents in organic synthesis through their application in a tandem 1,6-conjugate addition/enolate oxidation sequence. Reports of our progress toward a total synthesis of angelmicin B will be forthcoming.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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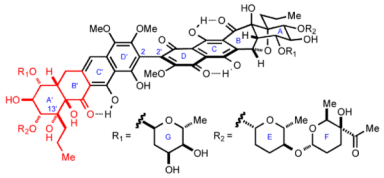
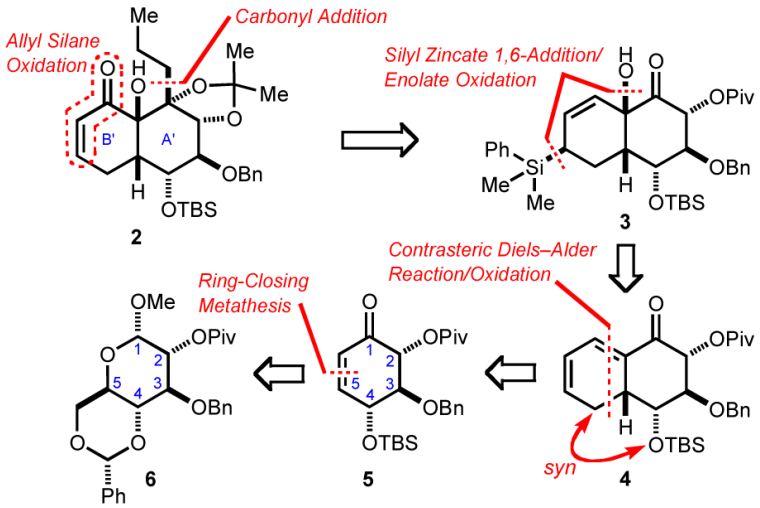
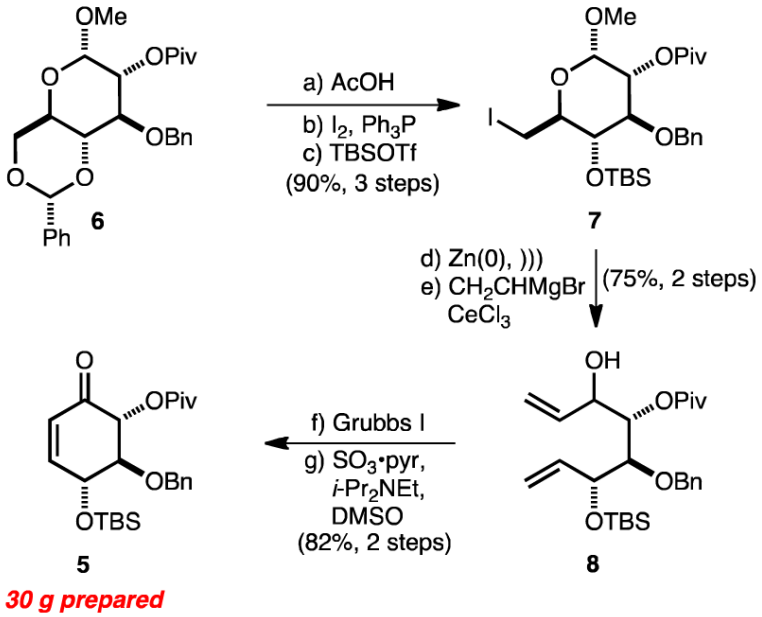


Figure 1.
Structure of angelmicin B (**1**)



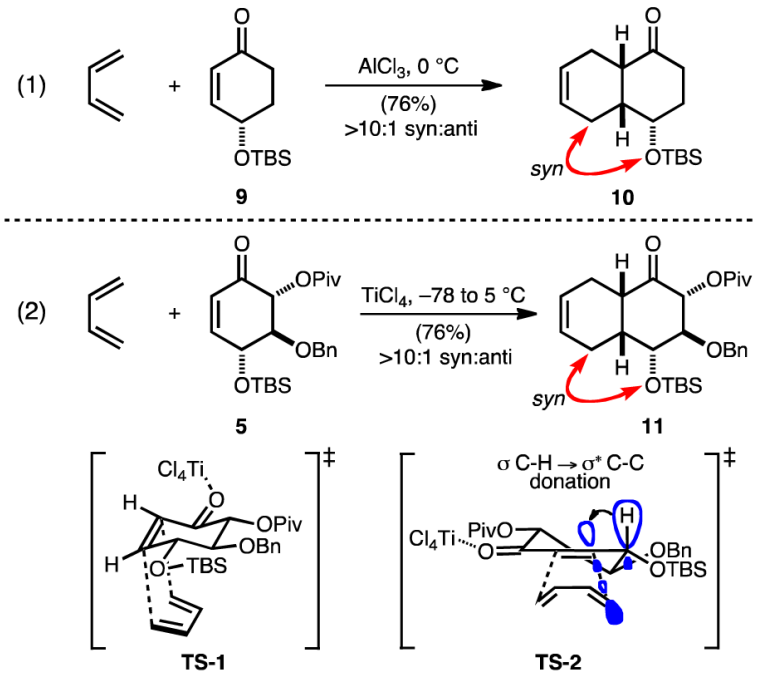
Scheme 1.
Proposed Synthesis of **2**



Scheme 2.

Synthesis of Diels–Alder Substrate **5**[a]

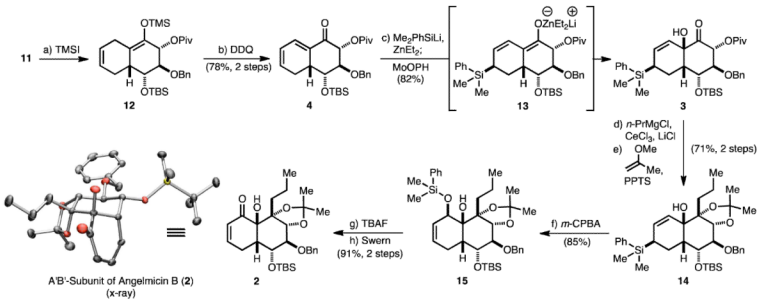
[a] Reagents and conditions: (a) 80% aq AcOH, 80 °C, 1 h, 94%; (b) Ph_3P (1.3 equiv), imidazole (3.0 equiv), I_2 (1.3 equiv), PhMe, 23 to 45 °C, 1 h, 97%; (c) TBSOTf (2.0 equiv), 2,6-lutidine (1.0 M), 0 to 23 °C, 30 min, 99%; (d) Zn(0) (10 equiv), THF/H_2O (4:1), sonication, 40 °C, 2 h; (e) $CH_2CHMgBr$ (1.2 equiv), $CeCl_3$ (1.2 equiv), THF, −78 °C, 2 h, 75% (3:1 dr) for two steps; (f) Grubbs I (5 mol %), CH_2Cl_2, 23 °C, 18 h, 85%; (g) SO_3•pyr (3.0 equiv), *i*-Pr_2NEt (5.0 equiv), DMSO (10.0 equiv), CH_2Cl_2, 0 °C, 1.5 h, 97%. Abbreviations: TBS = *tert*-butyldimethylsilyl, Grubbs I = bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride, DMSO = dimethyl sulfoxide, pyr = pyridine.



Scheme 3.

Lewis Acid-Catalyzed Contrasteric Diels–Alder Reaction[a]

[a] Reagents and condtions: (a) 1,3-butadiene (20 equiv), $AlCl_3$ (0.9 equiv), PhMe, 23 °C, 1 h, 76% (>10:1 *syn*:*anti*). (b) 1,3-butadiene (8.0 equiv), $TiCl_4$ (1.0 equiv), PhMe, −78 to 5 °C, 3.5 h, 76% (>10:1 *syn*:*anti*). Abbreviations: TS = transition state.



Scheme 4.

Completion of the Synthesis of the A'B'-Subunit of Angelmicin B (*2*)[a]

[a] Reagents and conditions: (a) TMSCl (10 equiv), NaI (15 equiv), HMDS (20 equiv), MeCN, 82 °C, 3 h; (b) DDQ (3.0 equiv), CH_2Cl_2, 23 °C, 3 h, 78% for two steps; (c) $Me_2PhSiLi$ (1.0 M in THF, 1.5 equiv), $ZnEt_2$ (1.0 M in PhMe, 1.5 equiv), THF, −78 °C, 30 min; then **4**, −78 to 0 °C, 30 min; then MoOPH (2.6 equiv), −78 to −20 °C, 20 min, 82%; (d) $CeCl_3$ (15 equiv), LiCl (30 equiv), THF, 23 °C, 12 h; then *n*-PrMgCl (1.6 M in Et_2O, 12 equiv), −78 °C, 3 h; then **3**, −78 to 0 °C, 2 h, 85%; (e) 2-methoxypropene (10 equiv), PPTS (10 mol %), PhH, 23 °C, 4.5 h, 84%; (f) *m*-CPBA (1.3 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, −78 to −5 °C, 7 h, 85%; (g) TBAF (1.0 M in THF, 1.5 equiv), THF, −78 °C, 1.5 h, 99%; (h) $(COCl)_2$ (8.0 equiv), DMSO (16 equiv), CH_2Cl_2, −78 °C, 1 h; then diol, −78 °C, 4 h; then Et_3N (32 equiv), −78 to 0 °C, 30 min, 92%. Abbreviations: TMS = trimethylsilyl, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, MoOPH = Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide), PPTS = pyridinium *p*-toluenesulfonate, *m*-CPBA = *meta*-chloroperbenzoic acid, TBAF = tetrabutylammonium fluoride.